General

Guideline Title

Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines.

Bibliographic Source(s)

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Monagle P, Chalmers E, Chan A, DeVeber G, Kirkham F, Massicotte P, Michelson AD. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):887S-968S. [561 references]

Recommendations

Major Recommendations

The grades of recommendation (1A, 1B, 1C, 2A, 2B, 2C) and the approach to rating the quality of evidence are defined at the end of the "Major Recommendations" field.

Antithrombotic Therapy in Pediatric Patients

The expert panel suggests that where possible, pediatric hematologists with experience in thromboembolism (TE) manage pediatric patients with TE (Grade 2C). When this is not possible, the expert panel suggests a combination of a neonatologist/pediatrician and adult hematologist supported by consultation with an experienced pediatric hematologist (Grade 2C).

Heparin in Neonates and Children

The expert panel suggests that therapeutic unfractionated heparin (UFH) in children is titrated to achieve a target range of anti-Xa activity of 0.35 to 0.7 units/mL or an activated partial thromboplastin time range that correlates to this anti-Xa range or to a protamine titration range of 0.2 to 0.4 units/mL (Grade 2C). The expert panel suggests that when initiating UFH therapy, UFH boluses be no greater than 75 to 100 units/kg and that boluses be withheld or reduced if there are significant bleeding risks (Grade 2C). The expert panel suggests avoiding long-term use of therapeutic UFH in children (Grade 2C).

Low-Molecular-Weight Heparin (LMWH) in Neonates and Children

The expert panel suggests, for neonates and children receiving either once- or twice-daily therapeutic LMWH that the drug be monitored to a target anti-Xa activity range of 0.5 to 1.0 units/mL in a sample taken 4 to 6 h after subcutaneous (SC) injection or 0.5 to 0.8 units/mL in a sample taken 2 to 6 h after SC injection (Grade 2C).

Vitamin-K Antagonists (VKAs) in Neonates and Children

The expert panel suggests, for children receiving VKAs, that the drug be monitored to a target international normalized ratio (INR) of 2.5 (range, 2.0-3.0), except in the setting of prosthetic cardiac valves where the expert panel suggests adherence to the adult recommendations outlined in the National Guideline Clearinghouse (NGC) summary of the American College of Chest Physicians (ACCP) guideline Antithrombotic and thrombolytic therapy for valvular disease (Grade 2C). The expert panel suggests that INR monitoring with point-of-care monitors be made available where resources make this possible (Grade 2C).

Aspirin

The expert panel suggests that when aspirin is used for antiplatelet therapy in children, it is used in doses of 1 to 5 mg/kg per day (Grade 2C).

Recommendations for Antithrombotic Therapy in Specific Clinical Situations

Venous Thromboembolism (VTE) in Neonates

The expert panel suggests that central venous access devices (CVADs) or umbilical venous catheters (UVCs) associated with confirmed thrombosis be removed after 3 to 5 days of therapeutic anticoagulation rather than left in situ (Grade 2C). The expert panel suggests either initial anticoagulation or supportive care with radiologic monitoring for extension of thrombosis rather than no follow-up (Grade 2C); however, in previously untreated patients, the expert panel recommends the start of anticoagulation if extension occurs (Grade 2C). The expert panel suggests that anticoagulation should be with either (1) LMWH or (2) UFH followed by LMWH. The expert panel suggests a total duration of anticoagulation of between 6 weeks and 3 months rather than shorter or longer durations (Grade 2C). If either a CVAD or a UVC is still in place on completion of therapeutic anticoagulation, the expert panel suggests a prophylactic dose of anticoagulation until such time as the CVAD or UVC is removed (Grade 2C). The expert panel suggests against thrombolytic therapy for neonatal VTE unless major vessel occlusion is causing critical compromise of organs or limbs (Grade 2C). The expert panel suggests if thrombolysis is required, tissue plasminogen activator (tPA) is used rather than other lytic agents (Grade 2C), and the expert panel suggests plasminogen (fresh frozen plasma) administration prior to commencing therapy (Grade 2C).

Renal Vein Thrombosis in Neonates

For unilateral renal vein thrombosis (RVT) in the absence of renal impairment or extension into the inferior vena cava (IVC), the expert panel suggests either (1) supportive care with radiologic monitoring for extension of thrombosis (if extension occurs the expert panel suggests anticoagulation) or (2) anticoagulation with UFH/LMWH or LMWH in therapeutic doses rather than no therapy. If anticoagulation is used, the expert panel suggests a total duration of between 6 weeks and 3 months rather than shorter or longer durations of therapy (Grade 2C). For unilateral RVT that extends into the IVC, the expert panel suggests anticoagulation with UFH/LMWH or LMWH for a total duration of between 6 weeks and 3 months (Grade 2C).

For bilateral RVT with evidence of renal impairment, the expert panel suggests anticoagulation with UFH/LMWH or initial thrombolytic therapy with tissue plasminogen activator (tPA) followed by anticoagulation with UFH/LMWH (Grade 2C).

Central Venous Access Device (CVAD) Prophylaxis in Neonates

For neonates with CVADs, the expert panel recommends to maintain CVAD patency with UFH continuous infusion at 0.5 units/kg per h over no prophylaxis (Grade 1A) or intermittent local thrombolysis (Grade 2C). For neonates with blocked CVADs, the expert panel suggests local thrombolysis after appropriate clinical assessment (Grade 2C).

Thromboprophylaxis for Blalock-Taussig Shunts and Modified Blalock-Taussig Shunts (MBTS)

For neonates and children having modified MBTS, the expert panel suggests intraoperative UFH therapy (Grade 2C). For neonates and children after MBTS surgery, the expert panel suggests either aspirin or no antithrombotic therapy as compared with prolonged LMWH or VKAs (Grade 2C).

Therapy for Femoral Artery Thrombosis in Neonates and Children

For neonates and children with acute femoral artery thrombosis, the expert panel recommends therapeutic doses of intravenous (IV) UFH as initial

therapy compared with aspirin or no therapy (Grade 1B) or LMWH (Grade 2C). The expert panel suggests subsequent conversion to LMWH, or else continuation of UFH, to complete 5 to 7 days of therapeutic anticoagulation as compared with a shorter or longer duration (Grade 2C).

For neonates and children with limb-threatening or organ-threatening (via proximal extension) femoral artery thrombosis who fail to respond to initial UFH therapy and who have no known contraindications, the expert panel recommends thrombolysis (Grade 1C). For neonates and children with femoral artery thrombosis, the expert panel recommends surgical intervention compared with UFH therapy alone when there is a contraindication to thrombolytic therapy and organ or limb death is imminent (Grade 1C).

Prophylaxis for Peripheral Arterial Catheters in Neonates and Children

For neonates and children with peripheral arterial catheters in situ, the expert panel recommends UFH continuous infusion at 0.5 units/mL at 1 mL/h compared with normal saline (Grade 1A).

Therapy for Peripheral Artery Thrombosis Secondary to Peripheral Artery Catheters in Neonates and Children

For neonates and children with a peripheral arterial catheter-related TE, the expert panel suggests immediate removal of the catheter (Grade 2B). For neonates and children with a symptomatic peripheral arterial catheter-related TE, the expert panel suggests UFH anticoagulation with or without thrombolysis or surgical thrombectomy and microvascular repair with subsequent heparin therapy (Grade 2C).

Prophylaxis of Umbilical Arterial Catheters in Neonates

For neonates with umbilical arterial catheters (UACs), the expert panel suggests UAC placement in a high rather than a low position (Grade 2B).

For neonates with UACs, the expert panel suggests prophylaxis with a low-dose UFH infusion via the UAC (heparin concentration of 0.25-1 unit/mL, total heparin dose of 25-200 units/kg per day) to maintain patency (Grade 2A).

Prophylaxis for Cardiac Catheterization (CC) in Neonates and Children

For neonates and children requiring CC via an artery, the expert panel recommends administration of IV UFH as thromboprophylaxis over no prophylaxis (Grade 1A) or aspirin (Grade 1B). For neonates and children requiring cardiac catheterization via an artery, the expert panel recommends the use of UFH doses of 100 units/kg as a bolus compared with a 50-unit/kg bolus (Grade 1B). In prolonged procedures, the expert panel suggests further doses of UFH rather than no further therapy (Grade 2B).

Cerebral Sinovenous Thrombosis in Neonates

For neonates with cerebral sinovenous thrombosis (CSVT) without significant intracranial hemorrhage (ICH), the expert panel suggests anticoagulation, initially with UFH or LMWH and subsequently with LMWH, for a total therapy duration between 6 weeks and 3 months rather than shorter or longer treatment duration (Grade 2C). For neonates with CSVT with significant hemorrhage, the expert panel suggests either (1) anticoagulation or (2) supportive care with radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus extension is noted as compared with no therapy (Grade 2C).

Arterial Ischemic Stroke in Neonates

For neonates with a first arterial ischemic stroke (AIS), in the absence of a documented, ongoing cardioembolic source, the expert panel suggests supportive care over anticoagulation or aspirin therapy (Grade 2C).

For neonates with a first AIS and a documented cardioembolic source, the expert panel suggests anticoagulation with UFH or LMWH (Grade 2C).

For neonates with recurrent AIS, the expert panel suggests anticoagulant or aspirin therapy (Grade 2C).

Neonates with Purpura Fulminans

For neonates with clinical presentations of homozygous protein C deficiency, the expert panel recommends administration of either 10 to 20 mL/kg of fresh frozen plasma every 12 h or protein C concentrate, when available, at 20 to 60 units/kg until the clinical lesions resolve (Grade 1A). For neonates with homozygous protein C deficiency, after initial stabilization, the expert panel recommends long-term treatment with VKA (Grade 1C), LMWH (Grade 1C), protein C replacement (Grade 1B), or liver transplantation (Grade 1C) compared with no therapy.

Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) in Children

In children with first VTE (CVAD and non-CVAD related) the expert panel recommends acute anticoagulant therapy with either UFH or LMWH (Grade 1B). The expert panel recommends initial treatment with UFH or LMWH for at least 5 days (Grade 1B). For ongoing therapy, the expert

panel suggests LMWH or UFH. For patients in whom clinicians will subsequently prescribe VKAs, the expert panel recommends beginning oral therapy as early as day 1 and discontinuing UFH/LMWH on day 6 or later than day 6 if the INR has not exceeded 2.0 compared with no therapy (Grade 1B).

The expert panel suggests that children with idiopathic VTE receive anticoagulant therapy for 6 to 12 months compared with no therapy (Grade 2C).

Underlying values and preferences: Families who place a high value on avoiding the unknown risk of recurrence in the absence of an ongoing risk factor and a lower value on avoiding the inconvenience of therapy or potential impact of therapy on growth and development and bleeding risk associated with antithrombotic therapy are likely to choose to continue anticoagulant therapy beyond 6 to 12 months.

In children with secondary VTE (i.e., VTE that has occurred in association with a clinical risk factor) in whom the risk factor has resolved, the expert panel suggests anticoagulant therapy be administered for 3 months (Grade 2C) as compared with no further therapy. In children who have ongoing, but potentially reversible, risk factors, such as active nephrotic syndrome or ongoing asparaginase therapy, the expert panel suggests continuing anticoagulant therapy beyond 3 months in either therapeutic or prophylactic doses until the risk factor has resolved (Grade 2C).

In children with recurrent idiopathic VTE, the expert panel recommends indefinite treatment with VKAs (Grade 1A).

In children with recurrent secondary VTEs with an existing reversible risk factor for thrombosis, the expert panel suggests anticoagulation until resolution of the precipitating factor but for a minimum of 3 months as compared with no further therapy (Grade 2C).

In children with a CVAD in place who have a VTE, if a CVAD is no longer required or is nonfunctioning, the expert panel recommends it be removed (Grade 1B). The expert panel suggests at least 3 to 5 days of anticoagulation therapy prior to its removal rather than no anticoagulation prior to removal (Grade 2C). If CVAD access is required and the CVAD is still functioning, the expert panel suggests that the CVAD remain in situ and the patient given anticoagulants (Grade 2C). For children with a first CVAD-related VTE, the expert panel suggests initial management as for secondary VTE as previously described.

In children with CVAD in place who have a VTE and in whom the CVAD remains necessary, the expert panel suggests, after the initial 3 months of therapy, that prophylactic doses of VKAs (INR range, 1.5-1.9) or LMWH (anti-Xa level range, 0.1-0.3 units/mL) be given until the CVAD is removed (Grade 2C). If recurrent thrombosis occurs while the patient is receiving prophylactic therapy, the expert panel suggests continuing therapeutic doses until the CVAD is removed and for a minimum of 3 months following the VTE (Grade 2C).

Thrombolysis in Pediatric Patients with DVT

In children with VTE, the expert panel suggests that thrombolysis therapy be used only for life- or limb-threatening thrombosis (Grade 2C). If thrombolysis is used in the presence of physiologically low levels or pathologic deficiencies of plasminogen, the expert panel suggests supplementation with plasminogen (Grade 2C). In children with VTE in whom thrombolysis is used, the expert panel suggests systemic thrombolysis or catheter-directed thrombolysis, depending on institutional experience and, in the latter case, technical feasibility.

Thrombectomy and IVC Filter Use in Pediatric Patients with DVT

In children with life-threatening VTE, the expert panel suggests thrombectomy (Grade 2C). In children who have had a thrombectomy, the expert panel suggests anticoagulant therapy as per the recommendations above under "DVT and PE in Children"(Grade 2C). In children >10 kg body weight with lower-extremity VTE and a contraindication to anticoagulation, the expert panel suggests placement of a retrievable IVC filter (Grade 2C). In children who receive a filter, the expert panel suggests that the filter be removed as soon as possible if thrombosis is not present in the basket of the filter and when contraindication to anticoagulation is resolved (Grade 2C). In children who receive an IVC filter, the expert panel recommends appropriate anticoagulation for VTE as soon as the contraindication to anticoagulation is resolved (Grade 1C).

DVT in Children with Cancer

In children with cancer, the expert panel suggests that management of VTE follow the general recommendations for management of VTE in children. The expert panel suggests the use of LMWH in the treatment of VTE for a minimum of 3 months until the precipitating factor has resolved (e.g., use of asparaginase) (Grade 2C).

Remarks: The presence of cancer, the need for surgery, chemotherapy, or other treatments may modify the risk-benefit ratio for treatment of VTE, and clinicians should consider these factors on an individual basis.

Children with Antiphospholipid Antibodies (APLAs) and DVT

For children with VTE in the setting of APLAs, the expert panel suggests management as per general recommendations for VTE management in

children.

Children with DVT and Positive Inherited Thrombophilia Testing

For children with VTE, independent of the presence or absence of inherited thrombophilic risk factors, the expert panel suggests that the duration and intensity of anticoagulant therapy as per the recommendations above under "DVT and PE in Children."

Children with VTE and Structurally Abnormally Venous Systems

For children with first VTE secondary to structural venous abnormalities, the expert panel suggests anticoagulation as per other "spontaneous" VTE (see recommendations above under "DVT and PE in Children") and consideration of subsequent percutaneous or surgical interventions, depending on patient factors and institutional experience. For children with recurrent VTE secondary to structural venous abnormalities, the expert panel suggests indefinite anticoagulation unless successful percutaneous or surgical interventions can be performed (Grade 2C).

Children with Right Atrial Thrombosis

For children with right atrial thrombosis related to CVAD, the expert panel suggests removal of the CVAD with or without anticoagulation, depending on the individual risk factors, compared with leaving the CVAD in situ (Grade 2C). For children with large (>2 cm) mobile right atrial thrombosis, the expert panel suggests anticoagulation, with appropriately timed CVAD removal, and consideration of surgical intervention or thrombolysis based on individualized risk-benefit assessment compared with no anticoagulation therapy (Grade 2C).

Children with CVADs

For CVADs, the expert panel suggests flushing with normal saline or heparin or intermittent recombinant urokinase to maintain patency as compared with no therapy (Grade 2C). For blocked CVADs, the expert panel suggests tPA or recombinant urokinase to restore patency (Grade 2C). If after at least 30 min following local thrombolytic instillation CVAD patency is not restored, the expert panel suggests a second dose be administered. If the CVAD remains blocked following two doses of local thrombolytic agent, the expert panel suggests radiologic imaging to rule out a CVAD-related thrombosis (Grade 2C).

For children with short- or medium-term CVADs, the expert panel recommends against the use of routine systemic thromboprophylaxis (Grade 1B).

For children receiving long-term home total parenteral nutrition, the expert panel suggests thromboprophylaxis with VKAs (Grade 2C).

Glenn Procedure or Bilateral Cavopulmonary Shunt (BCPS)

For children who have a BCPS, the expert panel suggests postoperative UFH (Grade 2C).

Fontan Surgery

For children after Fontan surgery, the expert panel recommends aspirin or therapeutic UFH followed by VKAs over no therapy (Grade 1C).

Endovascular Stents

For children having endovascular stents inserted, the expert panel suggests administration of UFH perioperatively (Grade 2C).

Dilated Cardiomyopathy

For pediatric patients with cardiomyopathy, the expert panel suggests VKAs no later than their activation on a cardiac transplant waiting list (Grade 2C).

Underlying values and preferences: Parents who place a high value on avoiding the inconvenience, discomfort, and limitations of anticoagulant monitoring and a lower value on the uncertain reduction in thrombotic complications are unlikely to choose VKA therapy for their children who are eligible for transplant.

Primary Pulmonary Hypertension

For children with primary pulmonary hypertension, the expert panel suggests starting anticoagulation with VKAs at the same time as other medical therapy (Grade 2C).

Biologic and Mechanical Prosthetic Heart Valves

For children with biologic or mechanical prosthetic heart valves, the expert panel recommends that clinicians follow the relevant recommendations

from the adult population (see the NGC summary of the ACCP guideline Antithrombotic and thrombolytic therapy for valvular disease).

Ventricular Assist Devices (VADs)

For children with VADs the expert panel suggests administration of UFH (Grade 2C). The expert panel suggests starting UFH between 8 and 48 h following implantation (Grade 2C). In addition, the expert panel suggests antiplatelet therapy (either aspirin or aspirin and dipyridamole) to commence within 72 h of VAD placement (Grade 2C). For children with VAD, once clinically stable, the expert panel suggests switching from UFH to either LMWH or VKA (target INR 3.0 range, 2.5-3.5) until transplanted or weaned from VAD (Grade 2C).

Primary Prophylaxis for Venous Access Related to Hemodialysis

For patients undergoing hemodialysis via an arteriovenous fistula, the expert panel suggests routine use of VKAs or LMWH as fistula thromboprophylaxis as compared with no therapy (Grade 2C).

For patients undergoing hemodialysis via CVAD, the expert panel suggests routine use of VKAs or LMWH for thromboprophylaxis as compared with no therapy (Grade 2C).

Use of UFH or LMWH during Hemodialysis

For children having hemodialysis, the expert panel suggests the use of UFH or LMWH during hemodialysis to maintain circuit patency independent of type of vascular access (Grade 2C).

Kawasaki Disease

For children with Kawasaki disease, the expert panel recommends aspirin in high doses (80-100 mg/kg per day during the acute phase for up to 14 days) as an antiinflammatory agent, then in lower doses (1-5 mg/kg per day for 6 to 8 weeks) as an antiplatelet agent (Grade 1B). For children with Kawasaki disease, the expert panel recommends IV γ-globulin (2 g/kg, single dose) within 10 days of the onset of symptoms (Grade 1A).

For children with moderate or giant coronary aneurysms following Kawasaki disease, the expert panel suggests that warfarin in addition to low-dose aspirin be given as primary thromboprophylaxis (Grade 2C).

For children with Kawasaki disease who have giant aneurysms and acute coronary artery thrombosis, the expert panel suggests thrombolysis or acute surgical intervention (Grade 2C).

CSVT in Children

For children with CSVT without significant intracranial hemorrhage, the expert panel recommends anticoagulation initially with UFH or LMWH and subsequently with LMWH or VKA for a minimum of 3 months relative to no anticoagulation (Grade 1B). In children who after 3 months of therapy still experience occlusion of CSVT or ongoing symptoms, the expert panel suggests administration of a further 3 months of anticoagulation (Grade 2C). For children with CSVT with significant hemorrhage, the expert panel suggests initial anticoagulation as for children without hemorrhage or radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus extension is noted at that time (Grade 2C). In children with CSVT and potentially recurrent risk factors (e.g., nephrotic syndrome, asparaginase therapy), the expert panel suggests prophylactic anticoagulation at times of risk factor recurrence (Grade 2C). The expert panel suggests thrombolysis, thrombectomy, or surgical decompression only in children with severe CSVT in whom there is no improvement with initial UFH therapy (Grade 2C).

AIS in Children

For children with acute AIS, with or without thrombophilia, the expert panel recommends UFH or LMWH or aspirin as initial therapy until dissection and embolic causes have been excluded (Grade 1C). For children with acute AIS, the expert panel suggests, once dissection and cardioembolic causes are excluded, daily aspirin prophylaxis for a minimum of 2 years as compared with no antithrombotic therapy (Grade 2C). For children receiving aspirin who have recurrent AIS or transient ischemic attacks (TIAs), the expert panel suggests changing to clopidogrel or anticoagulant therapy with LMWH or VKA (Grade 2C). For children with AIS, the expert panel recommends against the use of thrombolysis (tPA) or mechanical thrombectomy outside of specific research protocols (Grade 1C).

Embolic Stroke

For AIS secondary to cardioembolic causes, the expert panel suggests anticoagulant therapy with LMWH or VKAs for at least 3 months (Grade 2C). For AIS secondary to cardioembolic causes in children with demonstrated right-to-left shunts (e.g., PFO), the expert panel suggests surgical closure of the shunt (Grade 2C).

Dissection

For AIS secondary to dissection, the expert panel suggests anticoagulant therapy with LMWH or VKAs for at least 6 weeks (Grade 2C). Ongoing treatment will depend on radiologic assessment of degree and extent of stenosis and evidence of recurrent ischemic events.

Cerebral Vasculopathies

For children with acute AIS secondary to non-Moyamoya vasculopathy, the expert panel recommends UFH or LMWH or aspirin for 3 months as initial therapy compared with no treatment (Grade 1C). For children with AIS secondary to non-Moyamoya vasculopathy, the expert panel suggests ongoing antithrombotic therapy should be guided by repeat cerebrovascular imaging.

Moyamoya Disease

For children with acute AIS secondary to Moyamoya, the expert panel suggests aspirin over no treatment as initial therapy (Grade 2C).

For children with Moyamoya, the expert panel suggests they be referred to an appropriate center for consideration of revascularization.

Definitions:

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Approach to Rating Quality of Evidence

Study Design	Quality of Evidence	Lower if	Higher if
Randomized Trial →	High	Risk of bias -1 Serious -2 Very serious Inconsistency -1 Serious -2 Very serious Indirectness -1 Serious -2 Very serious Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible confounding +1 Would produce a demonstrated effect or +1 Would suggest a spurious effect when result show no effect
	Moderate		
Observational Study →	Low		
	Very Low		

Strength of the Recommendations Grading System

Grade of Recommendation*	Benefit vs. Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
Strong recommendation, high-quality evidence, Grade 1A	Benefits clearly outweigh risk and burdens or vice versa	Consistent evidence from randomized controlled trials (RCTs) without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect
Strong recommendation, moderate-quality evidence, Grade 1B	Benefits clearly outweigh risk and burdens or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on confidence in the estimate of effect and may change the estimate
Strong recommendation, low- or very-low-quality evidence, Grade 1C	Benefits clearly outweigh risk and burdens or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate

Grade of Recommendation*	Benefit vs. Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
Weak recommendation, high-quality evidence, Grade 2A	Benefits closely balanced with risks and burden	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient or society values. Further research is very unlikely to change confidence in the estimate of effect
Weak recommendation, moderate-quality evidence, Grade 2B	Benefits closely balanced with risks and burden	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	Best action may differ depending on circumstances or patient or society values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate
Weak recommendation, low- or very-low-quality evidence, Grade 2C	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate

*The guideline developers use the wording recommend for strong (Grade 1) recommendations and suggest for weak (Grade 2) recommendations.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Pediatric thromboembolism

Guideline Category

Management

Prevention

Treatment

Clinical Specialty

Cardiology

Critical Care

Emergency Medicine

Family Practice

Hematology

Neurology

Pediatrics

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

- To update evidence-based recommendations for the use of anticoagulant therapy for the management of thromboembolic conditions
- To offer guidance for many common anticoagulation-related management problems
- To optimize patient-important health outcomes and the processes of care for patients who have experienced or are at risk for thrombotic events
- To provide optimal strategies for the management of thrombosis in neonates and children

Target Population

Neonates and children (birth to 18 years) with or at risk for thromboembolism and requiring antithrombotic therapy

Interventions and Practices Considered

1. Vitamin K antagonists (VKA)
2. Unfractionated heparin (UFH)
3. Low-molecular-weight heparin (LMWH)
4. Aspirin
5. Dipyridamole
6. Clopidogrel
7. Monitoring
   - Anti-factor Xa assay
   - Activated partial thromboplastin time (aPTT)
   - International normalized ratio (INR)
   - Duration of anticoagulation therapy
   - Radiological monitoring for extension of thrombosis
8. Thrombolysis (urokinase, tissue plasminogen activator [tPA])
9. Plasminogen (fresh frozen plasma)
10. Thrombectomy
11. Catheter or access device removal
12. Surgical intervention
13. Inferior vena cava filter placement
14. Umbilical artery catheter placement
15. Intravenous (IV) gamma globulin, warfarin (for children with Kawasaki's disease)
16. Referral for revascularization (for children with Moyamoya)
17. Cerebrovascular imaging
18. Fresh frozen plasma, protein C concentrate, liver transplantation (for protein C deficiency)
19. Supportive care

Major Outcomes Considered

- Mortality
- Incidence and recurrence of thromboembolism

- Incidence of hemorrhage (major and central nervous system)
- Tissue loss
- Functional status
- Stroke or recurrent stroke
- Patency
- Valve replacement

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Defining the Clinical Questions—Population, Intervention, Comparator, and Outcome

The thrombosis expert on the Executive Committee along with the deputy editors took primary responsibility for defining the scope of the clinical questions that each article would address. For each question, the topic editor and deputy editor defined the relevant population, alternative management strategies (intervention and comparator), and the outcomes (i.e., population, intervention, comparator, and outcome [PICO] format). Each clinical question provided the framework for formulating study inclusion and exclusion criteria and guided the search for relevant evidence (systematic reviews and original studies). Panels typically restricted included studies to randomized controlled trials (RCTs) for intervention questions but included observational studies when there was a paucity of RCT data addressing an intervention and for questions of risk assessment. Readers can find these PICO questions in the first table of each article. One or more recommendations could be formulated for each clinical question.

Identifying the Evidence

To identify the relevant evidence, a team of methodologists and medical librarians at the Oregon Health & Science University Evidence-based Practice Center conducted literature searches of Medline, the Cochrane Library, and the Database of Abstracts of Reviews of Effects. For each article, the team conducted a search for systematic reviews and another for original studies encompassing the main populations and interventions for that article. These searches included studies indexed from week 1, January 2005, forward because Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th Edition (AT8) searches were carried out up to that date (search strategies are available on request). Many articles supplemented these searches with more-focused searches addressing specific clinical questions. When clinical questions had not been covered in AT8, searches commenced at a date relevant to each intervention.

Titles and abstracts retrieved from bibliographic database searches generally were screened in duplicate, and full-text articles were retrieved for further review. Consensus on whether individual studies fulfilled inclusion criteria was achieved for each study between two reviewers. If consensus could not be achieved, the topic editor and other topic panelists were brought into the discussion. Deputy editors reviewed lists of included studies from the database searches in order to identify any potentially missed studies. Additional studies identified were then retrieved for further evaluation.

Topic panels also searched the same bibliographic databases for systematic reviews addressing each PICO question. The quality of reviews was assessed using principles embodied in prior instruments addressing methodologic quality of systematic reviews, and wherever possible, current high-quality systematic reviews were used as the source of summary estimates. Reviews were also used to identify additional studies to complement the database searches.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Approach to Rating Quality of Evidence

Study Design	Quality of Evidence	Lower if	Higher if
Randomized Trial →	High	Risk of bias -1 Serious -2 Very serious Inconsistency -1 Serious -2 Very serious Indirectness -1 Serious -2 Very serious Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible confounding +1 Would produce a demonstrated effect or +1 Would suggest a spurious effect when result show no effect
	Moderate		
Observational Study →	Low		
	Very Low		

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Assessing Studies and Summarizing Evidence

Evaluating Risk of Bias in Individual Studies

The expert panel developed and applied uniform criteria for evaluating the risk of bias associated with individual randomized controlled trials (RCTs) based on the criteria recommended by the Cochrane Collaboration (Table 1 in the methodology companion [see the "Availability of Companion Documents" field]). Although all authors assessed risk of bias for individual studies, because of resource limitations, the panel summarized the results of the risk of bias for only a minority of the recommendations. Readers can find these assessments in the online data supplements. For most recommendations for which such tables were not developed, Evidence Profiles that typically provide information on the risk of bias in footnotes were developed.

The panel also developed specific criteria for assessing the risk of bias of observational studies (cohort studies with concurrent controls, cohort studies with historical controls, case-control studies, or case series). Again, these were based on the evidence-based domains recommended by the Cochrane Collaboration for observational studies.

Studies without internal comparisons were termed "cohort studies without internal controls" if they met the following criteria:

1. A protocol existed before the date of commencement of data collection.
2. A definition of inclusion and exclusion criteria was available.
3. The study reported the number of excluded patients.

4. The study conducted a standardized follow-up, including description of all of the following: schedule of follow-up, investigation of suspected outcomes, and criteria used to define outcomes.
5. The study reported all losses to follow-up.

The panel labeled studies that did not meet these criteria as "case series." No distinction was made between prospective and retrospective studies because although prospective studies may on average be of higher quality, individual prospective studies may have a significant risk of bias and specific retrospective studies may not. For questions related to risk assessment, the panel evaluated the risk of bias of individual studies using the following criteria: valid outcome assessment, including blinding when appropriate; adjustment for between-group differences; and minimal loss to follow-up.

Evaluating Quality of Bodies of Evidence

The expert panel assessed evidence across studies on an outcome-by-outcome basis using criteria suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. The expert panel defined quality of evidence as their confidence in the estimate of the effect to support a recommendation. RCTs start as high-quality evidence and observational studies as low-quality evidence. Additional factors that affect this rating of quality include the risk of bias; precision, consistency, and directness of results; likelihood of publication bias; and presence of very large effects. The American College of Chest Physicians (ACCP) adaptation of the GRADE system differs only in that the quality of a body of evidence can be high (A), moderate (B), or low (C); GRADE also provides a category for very-low-quality evidence. See the "Rating Scheme for the Strength of the Evidence" field.

Often, the panel found that the quality of the evidence differed across outcomes. For example, in assessing the quality of evidence for thienopyridines vs warfarin in patients undergoing percutaneous coronary interventions, the panel determined the evidence to be of moderate quality for mortality, nonfatal myocardial infarction, and revascularization but of low quality for major bleeding.

The panel then made a rating of the quality of the entire body of evidence bearing on the effect of alternative management strategies for each clinical question. In other words, the panel assessed the quality across outcomes, including both benefits and harms. Quality for each recommendation was the lowest quality rating of the outcomes judged as critical (as opposed to important, but not critical).

Most patient-important outcomes in this guideline are binary or yes-no outcomes (death, stroke, venous thromboembolism [VTE], myocardial infarction, bleeding). In general, relative effects are similar across subgroups of patients, including those with varying baseline risk. The evidence summaries (Evidence Profiles and Summary of Findings tables), therefore, include a presentation of relative effects (where possible as relative risks because they are easier to understand than odds ratios [ORs]) of intervention vs control management strategies.

Trading off desirable and undesirable consequences (e.g., thrombosis vs bleeding) requires, however, estimates of absolute effect. For example, in patients with atrial fibrillation, warfarin results in a 66% relative risk reduction in nonfatal stroke. This comes at a cost of inconvenience, lifestyle restrictions, and risk of bleeding. For patients with a CHADS (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke) score of ≥3, the 66% relative risk reduction translates into an absolute reduction of 6.3% (63 in 1,000) per year. Virtually all patients will consider this worthwhile. On the other hand, for patients with a CHADS score of 0, the 66% reduction translates into an absolute risk reduction of only 0.5% (5 in 1,000) per year. Many patients may consider this reduction not worth the undesirable consequences of warfarin use.

The panel calculated absolute effects by applying relative risks to estimates of control group risk. For instance, if control group risk of thrombosis is 4% and relative risk with an intervention is 50%, then the absolute difference between intervention and control is 4% of 50% or 2%, and the number needed to treat to prevent an episode of thrombosis is 100/2 or 50. In many cases, the Summary of Findings tables present effects as events prevented (or caused) per 1,000 patients. In this hypothetical example, the effect would be 20 events per 1,000 patients.

Whenever valid prognostic data were available from observational studies, they were used to estimate control group risks. When credible results from observational and prognostic studies were not available, risk estimates from control groups of RCTs were used.

Considering Subgroup-Specific Relative and Absolute Effects

Whenever the expert panel identified credible evidence that the relative effects vary across distinguishable subgroups of patients (i.e., interaction between the intervention and a patient characteristic), the respective relative effects were considered separately. The panel then calculated the associated absolute effects.

Even when the relative effect is the same, the absolute magnitude of treatment effects may differ in patients with varying levels of risk. For instance, although the relative risk reduction of warfarin vs aspirin in stroke prevention for patients with atrial fibrillation is likely close to 50% across risk groups, this translates into an absolute risk reduction of <1% per year in the lowest-risk groups and ~5% per year in the highest-risk groups.

The expert panel included control group risks and absolute-effect estimates for different groups in the summaries of effect when (and only when)

two conditions were present. First, they required validated prognostic models or, at the very least, credible strategies for clinicians to easily identify higher- and lower-risk patients. Second, the panel identified varying risk groups only when recommendations differed in strength or direction between groups. Both conditions were met, for instance, in the atrial fibrillation recommendations in which strong recommendations in favor of anticoagulation were restricted to the higher-risk patients.

Conducting Meta-analyses

When pooled estimates of effects were not available from existing high-quality systematic reviews, the panel performed meta-analyses if the data were sufficiently homogeneous. When pooling two studies, they used a fixed-effects model. When three or more studies were available for generating a pooled estimate, they used a random-effects model as the primary analysis and a fixed-effects model as a secondary analysis. If there were discrepancies between the two, the panel considered the following reasons: If there was substantial heterogeneity leading to wider confidence intervals (CIs) with the random-effects model, the panel considered that model more trustworthy, and if the discrepancy was due to a single large dominant study with a result substantially different from smaller studies, they considered the fixed-effects model more trustworthy. The panel also assessed statistical heterogeneity using both a χ^2 test and I^2 as well as assessed possible explanations of heterogeneity considering a priori-generated hypotheses.

Summary Tables

When resources permitted, the expert panel used a standardized approach for summarizing the evidence and methodology of individual studies. These summaries appear in the online data supplements. Wherever possible, the expert panel reported nonfatal events (e.g., nonfatal stroke) so that there is no overlap with the number of fatal events reported.

For a large number of recommendations, the expert panel summarized the quality of the body of evidence (see the "Rating Scheme for the Strength of the Evidence" field) and estimates of relative and absolute effect of alternative management strategies using the methods of the GRADE Working Group. Evidence Profiles summarize the quality of the body of evidence and when evidence comes from randomized trials, generally include a presentation of reviewer assessment of risk of bias, precision, consistency, directness, and publication bias associated with each outcome. As specified in GRADE methodology, the overall quality of evidence represents the lowest quality of any critical outcome.

Evidence Profiles can be found in the online data supplement. The format for these tables was determined through a formal survey of panelists that evaluated the panelists' preferences for alternative presentations and the impact of these presentations on their understanding of the evidence. The text in the printed version of Antithrombotic Therapy and Prevention of Thrombosis, 9th ed (AT9) recommendations includes more succinct Summary of Findings tables, which include the overall quality assessment as well as the relative and absolute effect sizes for each outcome. Use of an associated computer program facilitated the production of the Evidence Profiles and Summary of Findings tables which are listed in the original guideline document.

Methods Used to Formulate the Recommendations

Expert Consensus (Consensus Development Conference)

Description of Methods Used to Formulate the Recommendations

Composition and Selection of Topic Panel Members

The American College of Chest Physicians (ACCP) Antithrombotic Therapy and Prevention of Thrombosis, 9th ed (AT9) Executive Committee selected panel members for each article. A topic editor and a deputy editor led each of the AT9 panels issuing recommendations. The topic editor was the person primarily responsible for each article and was required to be a methodologist without serious financial or intellectual conflict of interest for any of the article's recommendations. In all but one case, the topic editor also was a clinician. The Executive Committee chose these individuals on the basis of their previous experience with guideline development and, in particular, their familiarity with methods developed by the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group. These topic editors and all panel members were approved by the ACCP Health and Science Policy (HSP) Committee after review of their conflict of interest disclosures.

Criteria for selection of the remainder of the panel members, including the deputy editor-thrombosis expert, were an established record in the relevant clinical or research area, international and gender representation, and an absence of financial conflicts of interest that were judged unacceptable. Some of the panelists had prior experience on ACCP guidelines in this area and represented the thrombosis community, but there was substantial turnover from the previous edition. After an international request for applications broadcast through multiple medical societies, the Executive Committee nominated individual topic editors and deputy editors and collaborated with them to identify and nominate other topic panel

members.

The ACCP HSP Committee reviewed all nominees and approved all panel members after review of their curricula vitae and conflict of interest disclosures. Of 150 nominees, 137 were approved, 18 were approved with management of conflicts of interest (i.e., regular disclosures and review of ongoing conflicts as the process progressed), and 13 were disapproved as a result of the magnitude of financial conflicts of interest. Articles associated with recommendations included from seven to 14 panel members. Patients or representatives of specific stakeholder groups were not included on topic panels.

Each topic panel also included a frontline physician working in the relevant area who was neither an expert in thrombosis nor a methodologist or clinical investigator. These individuals were chosen in consultation with the topic editors and the ACCP HSP Committee. These clinicians were charged with the following: (1) proposing important real-world clinical questions on the prevention, diagnosis, and treatment of thrombosis that were not addressed in Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, 8th Edition (AT8) and (2) reviewing the draft manuscripts and recommendations to assess the usability of the guidelines and the feasibility of implementation of AT9 recommendations.

To address issues of economic efficiency six health economist-physicians were included on the AT9 topic panels charged with making recommendations. These resource consultants were selected and approved through identical procedures to those for topic editors and panel members.

Ensuring Consistency Across Articles

A number of strategies were used to ensure consistency across articles, and one panel member participated extensively in the formulation of clinical questions for each article. To ensure consistency of judgments regarding bleeding, another panel member was responsible for standardizing the approach to bleeding outcomes and participated in multiple topic panels. Additionally, to ensure consistency in the trade-offs between thrombotic and bleeding events, all articles used the same ratings of values and preferences (described in more detail in the methodology companion [see the "Availability of Companion Documents" field]). Because some of the same evidence summaries were relevant to several articles, five individuals were chosen to participate in each of the articles addressing coronary artery disease, stroke, and peripheral arterial disease.

In AT9, prevention of venous thromboembolism (VTE) is addressed in three articles as opposed to a single article as was done in AT8. The prevention topic editors and deputy editors and those of the stroke article (which includes thromboprophylaxis recommendations) participated in multiple conference calls to develop and harmonize the approach to prevention and to ensure consistency among final recommendations. Topic editors consulted with one another when issues overlapped. For example, the decision regarding the use of a vitamin K antagonist, aspirin, and clopidogrel simultaneously in patients with atrial fibrillation, valvular disease, and intravascular stents is relevant for the atrial fibrillation, coronary, and peripheral arterial disease articles. Topic panels deferred to the Evidence-Based Management of Anticoagulant Therapy AT9 topic panel for recommendations related to the dosing and monitoring of anticoagulation therapies.

The AT9 Executive Committee met at least once a month and regularly issued statements of clarification of methods to topic editors and deputy editors (e.g., use of fixed- or random-effects models for meta-analysis), conflict of interest, preparation of tables, and issues of style and presentation. All these statements were communicated directly to the topic editors and deputy editors and made available in a central repository accessible to all AT9 panelists. The chair of the Executive Committee was available for resolving any challenging issues related to the aforementioned topics. Between September 2009 and September 2010, two members of the Executive Committee held regular (every 3 months), separate conference calls with each topic editor and deputy editor during which they addressed questions and concerns. Finally, the chair of the Executive Committee reviewed every article to ensure consistency of evidence presentation, evaluation, and writing style. Refer to the methodology companion for further information on the approach used to ensure consistent language in writing.

Formulating Recommendations

Following approaches recommended by the GRADE Working Group, the topic editor, in some cases aided by a panelist without conflicts, formulated the draft recommendations. The formulation of recommendations considered the balance between the desirable and undesirable consequences of an intervention; the quality of evidence; the variability in patient values and preferences; and, on occasion, resource use issues. The recommendations were graded as strong when desirable effects were much greater than undesirable effects or vice versa. Strong recommendations were worded as "The expert panel recommends" and labeled 1. Recommendations were graded as weak when desirable effects were not clearly greater or less great than undesirable effects. Weak recommendations were worded as "The expert panel suggests" and labeled 2. The rating of the quality of the evidence—high, A; moderate, B; or low, C—is provided with the strength of each recommendation.

Finalizing Recommendations

The topic panel members without primary conflicts discussed draft recommendations. Initial discussions generally led to a consensus at the article

level on the quality of evidence and the direction and strength of recommendations. At least two members of the Executive Committee reviewed in detail drafts of articles, including recommendations. Written critiques were prepared and returned to the authors for revision. Articles were then made available to the entire AT9 panel.

Recommendations on which topic panels had difficulty coming to a consensus were discussed at a final conference in February 2011 attended by the topic editors and deputy editors and at least one other panel member from each article. Prior to the conference, all AT9 panelists updated their conflict of interest disclosures. The ACCP invited a number of clinical organizations with interest in the guideline topic to attend the final conference as observers.

At this final conference, a representative of each article presented potentially controversial issues in their article's recommendations. Following discussion, which included those present and those attending by video conference, all panelists without primary conflicts of interest voted on each recommendation. The voting process used a GRADE grid and required that for a strong recommendation, ≥80% of those voting had to agree that a strong recommendation was appropriate.

The AT9 Executive Committee members harmonized the articles and resolved remaining disagreements among them through facilitated discussion with topic editors and deputy editors without primary conflicts. All major correspondence and decisions at the final conference were recorded in written and audio formats and are available on request to science@chestnet.org.

See the methodology companion (see the "Availability of Companion Documents" field) for information on accounting for patient values and preferences in recommendations.

Rating Scheme for the Strength of the Recommendations

Strength of the Recommendations Grading System

Grade of Recommendation*	Benefit vs. Risk and Burdens	Methodologic Quality of Supporting Evidence	Implications
Strong recommendation, high-quality evidence, Grade 1A	Benefits clearly outweigh risk and burdens or vice versa	Consistent evidence from randomized controlled trials (RCTs) without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect
Strong recommendation, moderate-quality evidence, Grade 1B	Benefits clearly outweigh risk and burdens or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on confidence in the estimate of effect and may change the estimate
Strong recommendation, low- or very-low-quality evidence, Grade 1C	Benefits clearly outweigh risk and burdens or vice versa	Evidence for at least one critical outcome from observational studies, case series, or from RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate
Weak recommendation, high-quality evidence, Grade 2A	Benefits closely balanced with risks and burden	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on circumstances or patient or society values. Further research is very unlikely to change confidence in the estimate of effect
Weak recommendation, moderate-quality evidence, Grade 2B	Benefits closely balanced with risks and burden	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	Best action may differ depending on circumstances or patient or society values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate
Weak recommendation, low- or very-low-quality evidence, Grade 2C	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or RCTs, with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate

Cost Analysis

Resource Use Issues

In addressing resource use (cost) issues in Antithrombotic Therapy and Prevention of Thrombosis, 9th ed (AT9), the expert panel followed previously developed principles. In particular, the panel restricted economic evaluation to recommendations in which it was plausible that resource use considerations might change the direction or strength of the recommendation and in which high-quality economic evaluations were available. When this was not the case, the panel did not consider resource use in the recommendations.

Six clinicians with the requisite expertise in decision and economic analyses participated in the guideline development process; each article had the benefit of one of these experts as a full committee member. The following subsections present key points in the process of considering resource allocation issues in the recommendations.

Overview of the Process

Panelists, in consultation with resource use consultants, determined questions for which resource use might change the direction or strength of recommendations. For those questions, the panel sought high-quality economic analyses. If such analyses were available, the panel applied the evidence regarding resource use to the relevant recommendation. If net costs or marginal cost-effectiveness ratios were very high, panelists considered rating down the quality of evidence for an intervention from high to low or possibly changing the direction of the recommendation using guides described in the section "Criteria for Resource Allocation Issues to Affect Recommendations—Thresholds for Cost-Effectiveness" in the methodology companion (see the "Availability of Companion Documents" field).

Identifying the Literature

The Oregon Health & Science University Evidence-based Practice Center conducted thorough literature searches for economic analyses relevant to the different AT9 articles. The resource use experts supplemented these by searches focused on the specific questions of interest for each article. The searches were conducted in Medline and the Cochrane Central Register of Clinical Trials. On the basis that data from studies appreciably more than a decade old would not reflect the current situation, searches were restricted to published studies from 1999 forward. Thus, bibliographic database searches encompassed publications from January 1999 forward: The end date varied across articles and ranged between November 2009 and March 2010 when the searches were executed.

Evaluating the Evidence

A standardized data extraction form was used to ensure uniform evaluation of the quality of relevant economic analyses. Quality assessment was based on published criteria and included specification of perspective of analysis (e.g., societal, health system), appropriateness of time horizon (preferably lifetime), use of high-quality evidence for probabilities and rates, use of high-quality sources for costs (e.g., primary data, Medicare payments, claims data as proxies), use of appropriate methods for measurement of preferences, and performance of sensitivity analyses to explore uncertainty (both deterministic and probabilistic).

Criteria for Resource Allocation Issues to Affect Recommendations—Thresholds for Cost-Effectiveness

The results of economic analyses may either increase the strength of an otherwise weak recommendation or weaken the strength of a strong recommendation. If cost-effectiveness studies bolstered an already strong recommendation, no change to the recommendation was necessary. The panel chose the following thresholds for cost-effectiveness considerations affecting recommendations:

1. When the clinical evidence warrants a strong recommendation for A over B:
    a. Strong recommendation favoring A when high-quality evidence from economic evaluations shows that A costs <3 times the gross domestic product (GDP) per capita (approximately US $150,000) per quality-adjusted life year (QALY) gained relative to B
    b. Weak recommendation favoring A when high-quality evidence from economic evaluations shows that A costs 3 to 5 times the GDP per capita (~$150,000-$250,000) per QALY gained relative to B
    c. Weak recommendation favoring B when high-quality evidence from economic evaluations shows that A costs >5 times the GDP per capita (~$250,000) per QALY gained relative to B
2. When the clinical evidence warrants a weak recommendation for A over B:
    a. Strong recommendation favoring A if A results in cost savings of >10% to 20% of the GDP per capita (~$5,000-$10,000) relative to B (Cost savings must represent all downstream costs and not just the actual cost of the intervention, and analysis must demonstrate a high level of confidence that there is a cost savings.)

b. Continued weak recommendation favoring A when B is marginally more costly than A (<10% the GDP per capita)

c. Continued weak recommendation favoring A when A costs 0 to 5 times the GDP per capita per QALY gained relative to B

d. Weak recommendation favoring B if A costs >5 times the GDP per capita (~$250,000) per QALY gained relative to B

Extension of Economic Analyses to Low- and Middle-Income Countries

Although certain interventions may be cost-effective in high-income countries (e.g., <$20,000 per QALY gained), in poor countries, $20,000 gained per QALY may be prohibitive. The choice of a threshold will vary depending on who is making resource allocation decisions. To facilitate the use of already published cost-effectiveness analyses, the World Health Organization (WHO), through its WHO-CHOICE (Choosing Interventions that are Cost Effective) program has used criteria suggested by the Commission on Macroeconomics and Health. Interventions that cost <1 times the average per-capita income for a given country or region per QALY gained are considered very cost-effective. Interventions that cost up to three times the average per-capita income per QALY gained are still considered cost-effective, whereas those that exceed this level are not considered to be cost-effective. To facilitate this process, WHO has developed tables of such threshold values for different regions and countries around the world. Thus, the thresholds discussed in the previous section have been defined in terms of GDP per capita. Although referencing thresholds for cost-effectiveness to average per-capita income in middle- and low-income countries can help to extend results of economic analyses performed in high-income countries, such analyses may be less relevant in low-income countries because of significantly different material and labor costs and, thus, may be difficult to extrapolate. Furthermore, the comparator strategies may not be feasible or customary in these locales.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The American College of Chest Physicians (ACCP) Health and Science Policy (HSP) Committee established a process for the thorough review of all ACCP evidence-based clinical practice guidelines. After final review by the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed (AT9) Executive Committee, the guidelines underwent review by the Cardiovascular and Pulmonary Vascular NetWorks of the ACCP, the HSP Committee, and the ACCP Board of Regents. The latter two groups had the right of approval or disapproval but usually worked with the topic panelists and editors to make necessary revisions prior to final approval. Both the HSP Committee and the Board of Regents identified primary reviewers who read the full set of articles, and the remaining HSP Committee members were responsible for reviewing several articles each. The reviewers considered both content and methodology as well as whether there was balanced reporting and adherence to HSP Committee processes. All reviewers were vetted through the same conflict of interest disclosure and management process described in the "Description of Methods Used to Formulate the Recommendations" field. Finally, the Editor in Chief of *CHEST* read and forwarded the manuscripts for independent, external peer review prior to acceptance for publication. No recommendations or assessments of the quality of the evidence could be changed without the express approval of the topic panel members, AT9 Executive Committee, HSP Committee, and ACCP Board of Regents.

This guideline is endorsed by the American Association for Clinical Chemistry, the American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, the American Society of Hematology, and the International Society on Thrombosis and Haemostasis.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Potential Harms

- *Adverse effects of aspirin*: Neonates may be exposed to aspirin because of maternal ingestion (e.g., treatment of preeclampsia). Clearance of aspirin is slower in neonates, potentially placing them at risk for bleeding for longer periods of time. However, in vitro studies have not demonstrated an additive effect of aspirin on platelet hypofunction in newborns, and evidence linking maternal aspirin ingestion to bleeding in newborns is weak. In neonates, additive antiplatelet effect must be considered if concurrent indomethacin therapy is required. In older children, aspirin rarely causes important hemorrhage, except in the presence of an underlying hemostatic defect or in children also treated with anticoagulants or thrombolytic therapy. The relatively low doses of aspirin used as antiplatelet therapy, compared with the much higher doses used for antiinflammatory therapy, seldom cause other side effects. For example, although aspirin is associated with Reye syndrome, this appears to be a dose-dependent effect of aspirin and usually is associated with doses >40 mg/kg.
- *Adverse effects of clopidogrel*: Clinically significant bleeding episodes were infrequent in the PICOLO trial. High rates of excessive skin bruising have been reported when clopidogrel is used in combination with aspirin, and major bleeding is reported in children receiving concomitant warfarin therapy. Other studies have reported lower rates, but all studies to date have been small and retrospective. Overdose has been reported with minimal adverse effects.
- *Adverse effects of thrombolytic therapy*: Thrombolytic therapy has significant bleeding complications in children. Early literature reviews (including 255 patients) reported an incidence of bleeding requiring treatment with packed red blood cells (RBCs) of ~20%. The most frequent problem was bleeding at sites of invasive procedures. A large single-institution study reported bleeding in 68% of patients, with bleeding requiring transfusion occurring in 39%. Prolonged duration of thrombolytic infusion was associated with increased bleeding.
- *Adverse effects of heparin*: A common cause of fatal heparin-induced bleeding is accidental overdose, especially in neonates. The most common cause of this is drug error, with 5,000 units/mL or similar concentration vials being erroneously selected instead of 50 units/mL vials. The different uses of heparin in neonatal populations (from line flushes to extracorporeal circuit support) usually mean that vastly different-strength heparin doses are readily available to ward staff. Although rarely reported in the medical literature, the number of cases reported in the popular press appears to be increasing. There are only three case reports of pediatric unfractionated heparin (UFH)-induced osteoporosis. In two of these, the patients had additional risk factors before this complication. These limited data, in conjunction with adult data, would support avoidance of long-term use of UFH in children when alternative anticoagulants are available. This recommendation is strengthened by the physiologic changes in bone seen in childhood, which potentially places children at increased risk of osteoporosis compared with adults. As in adults, the diagnosis of heparin-induced thrombocytopenia (HIT) in children remains problematic.
- *Adverse effects of low-molecular-weight heparin (LMWH)*: A recent review of enoxaparin in neonates reported that minor side effects were common; major bleeding was recorded in 13 of 240 (5%) neonates. Whether premature infants are at increased risk is unclear. No major bleeds were reported in a series of 10 premature neonates. A review reported that in 308 children treated with therapeutic LMWH for venous thrombosis, nine (2.9%) had major bleeding, and 72 (23.4%) had minor bleeding. However, at least one of these studies included neonates. The same review reported that of 133 children treated with prophylactic doses of LMWH for primary prevention of venous thrombosis, one (0.8%) had major bleeding, and four (3.0%) had minor bleeding. There are no data addressing the frequency of osteoporosis, HIT, or other hypersensitivity reactions in children exposed to LMWH.
- *Adverse effects of vitamin K antagonists (VKAs)*: Bleeding is the main complication of VKA therapy. The risk of serious bleeding in children receiving VKAs for mechanical prosthetic valves, as calculated across 13 case series, is <3.2% per patient-year. In one large cohort (comprising 391 patient-years with variable target international normalized ratio [INR] ranges), the major bleeding rate was 0.5% per patient-year. Nonhemorrhagic complications of VKAs, such as tracheal calcification or hair loss, have been described on rare occasions in young children. Two cohort studies described reduced bone density in children receiving warfarin for >1 year. However, these were uncontrolled studies, and the role of the underlying disorders in reducing bone density remains unclear.

Contraindications

Contraindications

Contraindications to Thrombolysis in Neonates and Children

Specific contraindications for children have been described in one reported study, which included prematurity (<32 weeks gestation). However, thrombolytics have been successfully given to increasingly premature babies; the number of such patients remains small. Clinicians should, in each

case, make an individual assessment of the risk-benefit ratio of thrombolysis.

Qualifying Statements

Qualifying Statements

- The evidence-based practice guidelines published by The American College of Chest Physicians ("ACCP") incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Guidelines are intended for general information only, are not medical advice, and do not replace professional medical care and physician advice, which always should be sought for any specific condition. Furthermore, guidelines may not be complete or accurate because new studies that have been published too late in the process of guideline development or after publication are not incorporated into any particular guideline before it is disseminated. The ACCP and its officers, regents, governors, executive committee, members and employees (the "ACCP Parties") disclaim all liability for the accuracy or completeness of a guideline, and disclaim all warranties, express or implied. Guideline users always are urged to seek out newer information that might impact the diagnostic and treatment recommendations contained within a guideline. The ACCP Parties further disclaim all liability for any damages whatsoever (including, without limitation, direct, indirect, incidental, punitive, or consequential damages) arising out of the use, inability to use, or the results of use of a guideline, any references used in a guideline, or the materials, information, or procedures contained in a guideline, based on any legal theory whatsoever and whether or not there was advice of the possibility of such damages.
- Through a comprehensive and systematic literature review, the ACCP's evidence-based clinical practice guidelines incorporate data from the existing peer-reviewed literature. This literature meets the prespecified inclusion criteria for the clinical research question, which ACCP considers, at the time of publication, to be the best evidence available for general clinical information purposes. This evidence is of varying quality from original studies of varying methodological rigor. The ACCP recommends that performance measures for quality improvement, performance-based reimbursement, and public reporting purposes should be based on rigorously developed guideline recommendations. However, not all recommendations graded highly according to the ACCP grading system (1A, 1B) are necessarily appropriate for development into such performance measures, and each one should be analyzed individually for importance, feasibility, usability, and scientific acceptability (National Quality Forum criteria). Performance measures developers should exercise caution in basing measures on recommendations that are graded 1C, 2A, 2B, and 2C, according to the ACCP Grading System as these should generally not be used in performance measures for quality improvement, performance-based reimbursement, and public reporting purposes.
- Limitations of Methods: Although encouraged to use Evidence Profiles and Summary of Findings tables for all recommendations, there were some for which the authors were unable to produce such tables. However, those recommendations used an evidence-based systematic review and assessment of relevant studies. Some recommendations would have benefited from meta-analyses that would have clarified aspects of the evidence. Although panelists were instructed in completing the value and preference rating exercise to estimate patient values and preferences rather than to use their own, it cannot be assured that they succeeded in all instances.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Monagle P, Chan AK, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Gottl U, Vesely SK. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012 Feb;141(2 Suppl):e737S-801S. [767 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2001 Jan (revised 2012 Feb)

Guideline Developer(s)

American College of Chest Physicians - Medical Specialty Society

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The sponsors played no role in the development of these guidelines. Sponsoring organizations cannot recommend panelists or topics, nor are they allowed prepublication access to the manuscripts and recommendations.

Guideline Committee

American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel

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Financial Disclosures/Conflicts of Interest

All panelists were required to disclose both financial conflicts of interest, such as receipt of funds for consulting with industry, and intellectual conflicts of interest, such as publication of original data bearing directly on a recommendation. Financial and intellectual conflicts of interest were classified as primary (more serious) or secondary (less serious). The operational definition of primary intellectual conflicts of interest included authorship of original studies and peer-reviewed grant funding (government, not-for-profit organizations) directly bearing on a recommendation. The operational definition of primary financial conflicts of interest included consultancies, advisory board membership, and the like from industry. Topic editors had no primary conflicts of interest, as noted. Some deputy editors, who were clinical experts in the topic of the article, had relevant primary conflicts of interest. The American College of Chest Physicians (ACCP) Health and Science Policy (HSP) Committee deemed some of these conflicts serious enough to require "management." Management involved more frequent updates of disclosures than required of the approved panelists without any conflicts and recusal from activities relevant to that conflict.

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In summary, the authors have reported to *CHEST* the following conflicts of interest: Dr Goldenberg has received an NIH career development award and an investigator-initiated study grant from Eisai Co., Ltd. He is also Chair of the steering committee for a Phase II study of Dalteparin for Eisai Co. and Chair of a data monitoring committee for Bristol-Myers Squibb. Dr Ichord is a member of the Clinica Event Committee for Berlin Heart's IDE trial of the EXCOR-Pediatric (pediatric ventricular assist device). This involved reimbursement for travel expenses for study meetings and for time spent on committee meetings for a total financial reimbursement or <$1,000/y from 2007 to 2012. Drs Monagle, Chan, and Nowak-

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Guideline panel members, including the chair, and members of the Health & Science Policy Committee are blinded to the funding sources. Further details on the Conflict of Interest Policy are available online at http://chestnet.org _____.

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Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Monagle P, Chalmers E, Chan A, DeVeber G, Kirkham F, Massicotte P, Michelson AD. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008 Jun;133(6 Suppl):887S-968S. [561 references]

Guideline Availability

Electronic copies: Available to subscribers of Chest - The Cardiopulmonary and Critical Care Journal _____.

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

Availability of Companion Documents

The following are available:

- Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;7S-47S.
- Introduction to the ninth edition: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical guidelines. Chest 2012;141;48S-52S.
- Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;53S-70S.
- Patient values and preferences in decision making for antithrombotic therapy: a systematic review: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;e1S-e23S.
- Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;e44S-e88S.
- Antiplatelet drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;e89S-e119S.
- New antithrombotic drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;e120S-e151S.
- Approach to outcome measurement in the prevention of thrombosis in surgical and medical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141;e185S-e194S.

Electronic copies: Available to subscribers of Chest - The Cardiopulmonary and Critical Care Journal [   ].

Print copies: Available from the American College of Chest Physicians, Products and Registration Division, 3300 Dundee Road, Northbrook IL 60062-2348.

Patient Resources

None available

NGC Status

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